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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/724,571	11/28/2000	John P. Anderson	015270-006444US	6100

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EXAMINER
WALICKA, MALGORZATA A

ART UNIT	PAPER NUMBER
1652	15

DATE MAILED: 05/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

SM

Office Action Summary	Application No.	Applicant(s)	
	09/724,571	ANDERSON ET AL.	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 January 2003* .

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-134* is/are pending in the application.

4a) Of the above claim(s) *1-77,79 and 86-134* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *78 and 81-85* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet* .

Continuation of Attachment(s) 6). Other: Summary of the interview of August 9, 2002..

The Response to Restriction Requirement filed on September 11, 2002 as paper No. 10 and Amendment Filed on Jan.21, 2003, paper No. 14, are acknowledged.

The amendment to the claims has been entered as requested. Claims 78, 81, 84, and 85 are amended, new claims 132-134 are added. Claims 1-134 are pending in the application. Claims 78 and 81-85 are currently under examination and are the subject of this Office Action.

DETAILED ACTION

1. Election/Restriction

The examiner acknowledges the response to restriction requirement, papers No. 8, 10 and 14. Applicants, in response to restriction requirement issued by the previous examiner, elected with traverse Group V, Claims 78, 81-85.

The restriction requirement issued by the previous examiner divides claims 78-90 in the following way:

Group IVp. Claims 78-80, 84-85, drawn to a method for screening undisclosed compounds for inhibition of Aβ production in cells;

Group Vp. Claims 78, 81-85, drawn to a method for screening undisclosed compounds for inhibition of Aβ production in mammalian subject;

Group VIp. Claims 86-90, drawn to a method for screening compounds that inhibit Aβ production wherein the beta-secretase substrate is inhibitor of beta-secretase activity.

To clarify the division of claims between these groups including amendments to

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Group VIp. Claims 86-90, drawn to a method for screening compounds that inhibit Aβ production wherein the beta-secretase substrate is inhibitor of beta-secretase activity.

To clarify the division of claims between these groups including amendments to

claims filed in July 2002 and November 2002, i.e., after restriction requirement, Applicants attention is drawn to the following. Claim 79 should belong to both, Group IV and V. The newly filed claim 132 belongs to Group IV and V, and the newly filed claims 133 and 134 belong to Group VI. Therefore, the proper restriction requires that the three groups of inventions comprise the following claims:

Group IV. Claims 78-80, 84-85 and 132, drawn to a method for screening undisclosed compounds for inhibition of Aβ production in vitro;

Group V. Claims 78-80, 81-85 and 132, drawn to a method for screening undisclosed compounds for inhibition of Aβ production *in vitro* and *in vivo*, using a transgenic mammal;

Group VI. Claims 86-90, 133 and 134, drawn to a method for screening compounds that inhibit Aβ production wherein the beta-secretase substrate is inhibitor of beta-secretase activity.

In their response to restriction requirement filed in July 2002 as paper No. 8, Applicants elected with traverse, Group Vp consisting of claims 78, 81-85. Applicants arguments are, that Group IVp consists of claims 78-80 and 84-85; and Group V consists of claims 78, and 81-85. The result is that claims 78, 84, and 85 have been restricted into two groups, i.e., Groups IVp and Group Vp. Election of Group IV and prosecution of claims 78, 84, and 85 in one application and election of Group V and prosecution of claims 78, 84 and 85 in different application might result in claims 78, 84 and 85 issuing in two separate patents for the same invention. Furthermore Applicants state, "It is respectfully submitted that it is self–evident and incontrovertible that the restriction of

claims 78, 84 and 85 into Groups IV and V [Groups IVp and Vp, MW] is improper."

Applicants' arguments have been fully considered but they are found not persuasive. Group IV and V are different invention although they have a common part that is claimed in claims 78-80, 84-85 and 132. Thus restriction between inventions IV and V as written above is proper and made FINAL.

During the interview on August 9, 2002 the examiner requested election of species of beta-secretase and species of substrate to be used in the method. In response to this requirement, filed on September 11, 2002 as paper No. 10, Applicants elected beta-secretase of SEQ ID NO: 75, and as the species of substrate SEQ ID NO: 104, 83, and 97. In the supplemental response to restriction requirement filed on Jan. 21 as paper No. 14 Applicants mention only two species of the beta-secretase substrate, i.e., SEQ ID NO: 104 and SEQ ID No: 83.

Upon the allowance of a generic claim, Applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Claims 1-134 are pending in the application. Invention of Group V, claims 78-80, 81-85 and 132, is elected; elected species of beta- secretase is SEQ ID NO: 75; elected species of beta-secretase substrate are SEQ ID NO: 104 and 83. In result of the election of species claims 79, 80 and 132 are withdrawn from consideration as directed to the nonelected species of beta-secretase and its substrates. Thus, claims 78, 81-85

are the subject of this Office Action, claims 1-77, 79, 86-134 are withdrawn from consideration as drawn to the nonelected invention; see 37 CFR 1.142(b).

2. Objections

2.1. Specification

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors in the specification of which applicant may become aware.

The abbreviations Aβ in claim 78 and APP and APPsw in claim 84 should be expanded, because they are used in claims for the first time.

2. Rejections

2.1. 35 USC, section 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 81 and 82 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The scope of the claims includes use of a transgenic human being as a species in the genus of mammalian species

comprising a transgene. This rejection may be overcome by amending the claims to contain wording such as "A mammal excluding human ..."

2.2. 35 USC, section 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 78, and 81-83 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "fewer than about 450" in claim 78 is a phrase that renders the claim indefinite. The phrase is confusing in view of the use of the terms "fewer" and "about" together. "Fewer" implies less than, only, while "about" would include values greater than 450 amino acids. These terms are inconsistent.

2.3. 35 USC, section 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which

it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2.3.1. Lack of written description

Claim 82 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 82 recites a mammalian species comprising a transgene. No structure and function of said transgene is recited by the claim. The claim is generic, because it is directed to extremely large and variable genus of all genes currently known to used in transformation of mammalian cells.

Neither the specification nor the claims teach an identifying characteristics of said transgene, therefore one skilled in the relevant art is not convinced that the inventor(s), at the time the application was filed, had possession of the claimed invention.

2.3.2. Scope of enablement

Claim 78, 81-85 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *in vitro* testing, does not reasonably provide enablement for *in vivo* testing. The specification does not enable any person skilled in

the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claims are directed to the method of *in vitro* and *in vivo* testing a chemical compound for its ability to inhibit beta-secretase, wherein the *in vitro* part of the method uses as substrates of said beta-secretese polypeptides of SEQ ID NO:104 and 83.

In vivo testing, performed on transgenic animal, especially a mouse that encompasses a DNA molecule that encodes a human beta-amyloid precursor protein, uses as a proof of inhibiting of Aβ production an improvement of cognitive ability or reduced plaque burden.

The specification fails to disclose the steps of the method of the claims 81, particularly the way the tested compound is to be administered to a mammal and how to measure the cognitive abilities and plaque burden. Claim 82 and 83 lack the teaching how to obtain a transgenic mammal and in particularly how to make a transgenic mammal such as a mouse that comprises the human beta-amyloid precursor protein. Therefore, to make and use the claimed invention undue experimentation is necessary.

Factors to be considered in determining whether undue experimentation is required are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention encompasses a test using any mammal characterized by Aβ peptide deposits. This includes a mouse that additionally has to be transfected with a gene encoding a human β-amyloid precursor protein or its variant. The claims are also directed to the extremely large number of chemical molecules, as any chemical compounds is to be administered. Assessment of the treatment efficacy comprises measuring "cognitive ability", which is a generic term including several species, none of them is taught by applicants.

Although the studies of Alzheimer disease are well developed and the skill of artisans high, no one is able;

a) to test all animals for the level of Aβ peptide deposit, and select any one having the high level of said deposit, and/or choose a mouse with high level of Aβ peptide deposit and produce from it a transgenic species comprising a human β-amyloid precursor protein,

b) to develop the way of administration to said animal of <u>any chemical compound that can be considered as a candidate inhibitor</u> of β-secretase; said way includes finding the proper solvent, dose, frequency and time of administration to avoid lethal effects and diminish side effects,

c) to measure the level of Aβ peptide deposits and/or cognitive ability of the treated animal before and after the appropriate time of treatment.

The disclosure is silent about any of the steps a)-c). Without further guidance on the part of applicants regarding the experimental animal and chemical compound to be used, as well as without teaching the details of the compound administration and

measurements of the level of Aβ peptide deposits and measurements of cognitive abilities experimentation being left to the skilled artisan has a low probability of success. The experimentation is therefore, improperly extensive and undue.

2.4. *35 USC section 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 78, 81-85 are rejected under 35 U.S.C. 103(a) as being unpatentable over International Publication Number WO96/40885 (WO85), issued December 19, 1996; International Publication Number WO 98/37226 (WO26) issued 27 August 1998, and further in view of US Patent No. 6,319,689, issued to Powell et al on Nov. 20, 2001, with priority date Jan. 28, 1997.

The claims are directed to a method of screening for inhibitors of Aβ production comprising contacting a β-secretase polypeptide, wherein the polypeptide is purified to apparent homogeneity, and comprises a polypeptide that

(i) is fewer than about 450 amino acid residues in length,

(ii) includes an amino acid sequence that is at least 90% identical to SEQ ID NO: 75 including conservative substitutions thereof, and

(iii) exhibits β-secretase activity, as evidenced by an ability to cleave a substrate selected from the group consisting of the 695 amino acid isotype of beta amyloid precursor protein (βAPP) between amino acids 596 and 597 thereof, MBP-C125wt (SEQ ID N): 103) and MBPsw (SEQ ID NO: 104),

with a β-secretase substrate, and a test compound and selecting the test compound as capable of inhibiting Aβ production if said β-secretase polypeptide exhibits less β-secretase activity in the presence of said compound than in the absence of said compound.

WO85 discloses a method for identifying inhibitors of β-secretase, see the abstract and the method description on page 44, in which peptide Val-Asn-Leu-Asp, i.e., SEQ ID NO: 104 of the instant application, is used as a substrate (Fig. 4 of WO85). The WO85 uses partially purified β-secretase.

WO85 does not disclose:

(1) the β-secretase purified to the apparent homogeneity;

(2) substrate set forth by SEQ ID NO: 83, used in claim 85, in the instant application; and

(3) β-secretase polypeptide comprising a polypeptide that

(i) is fewer than about 450 amino acid residues in length

(ii) includes an amino acid sequence that is at least 90% identical to SEQ ID NO: 75 including conservative substitutions thereof, and

(iii) exhibits β-secretase activity, as evidenced by an ability to cleave a substrate selected from the group consisting of the 695 amino acid isotype of beta amyloid precursor protein (βAPP) between amino acids 596 and 597 thereof, MBP-C125wt (SEQ ID N): 103) and MBPsw (SEQ ID NO: 104).

Regarding point (1), the fact that β-secretase is purified to the apparent homogeneity is not a characteristic feature of the enzyme as such, unless the inventors disclose a new method specifically directed to purification of β-secretase, this, however, is not the case.

Regarding point (2), i.e., the substrate recited by claim 85, WO26 discloses compositions for the detecting protease activity in biological samples, and, on page 28, and in claim 4 on page 77, presents as a substrate consisting of the amino acid sequence SEVNLDAEF described as "Swedish KM/NL amyloid". This sequence is identical to SEQ ID NO: 83 of the instant application, thus, WO26 anticipates SEQ ID NO: 83 of the instant application.

With respect to point (3), Powell discloses the full amino acid sequence, i.e. 501 amino acids, of human β-secretase of SEQ ID NO: 2. This 501 amino acid sequence comprises the sequence that

(i) is fewer than about 450 amino acid residues in length,

(ii) includes an amino acid sequence that is at least 90% identical to SEQ ID NO: 75.

Powell does not disclose that the full length human β-secretase of SEQ ID NO: 2 cleaves a substrate selected from the group consisting of the 695 amino acid isotype of beta amyloid precursor protein (βAPP) between amino acids 596 and 597 thereof, MBP-C125wt (SEQ ID N): 103) and MBPsw (SEQ ID NO: 104). However, these features are the characteristic features of the human β-secretase determined by its amino acid sequence identified by SEQ ID NO: 2 in the patent. The same sequence, also identified in the instant application as SEQ ID NO: 2, is used by the instant inventors the produce its active truncated forms. One of the active fragment is identified in the instant application by SEQ ID NO: 75. Thus, the β-secretase genus recited by claim 78 comprises the species that is anticipated by Powell et al. in the Patent.

It would have been obvious to one having ordinary skill in the art at the time of invention to have the method disclose in WO85 and modify it by using the purified human β-secretase as disclosed by Powell and the substrate of SEQ ID NO: 83 as disclosed by WO26.

The motivation is also provided by the WO85 2: "the putative β-secretase enzyme would permit chemical modeling of a critical event in the pathology of

Alzheimer's disease and would allow the screening of compounds to determine their ability to inhibit β-secretase activity" (page 2 line 2), and further, on page 2 line 9, "In particular, it would be desirable to utilize such an enzyme (referred to hereinafter as β-secretase) in methods for screening candidate drug for the ability to inhibit the activity of β-secretase in *in vitro* systems."

The motivation regarding the use as a substrate "Swedish KM/NL amyloid" sequence is also provided by WO85: "A mutation of particular interest is designated the 'Swedish' mutation where the normal Lys-Met residues at positions 595 and 596 of the 695 form are replaced by Asn-Leu. This mutation is located directly upstream of the normal β-secretase cleavage site of APP, which occurs between residues 596 and 597 of the 695 form" (page 9, line 23).

The probability of success is 100%, because the probability of identifying any β-secretase inhibitor using a modified method of WO85 is 100%.

Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made, and was, as a whole, *prima facie* obvious.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number is (703) 305-7270. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m.

If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (703) 308-3804. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 308-0196.

Malgorzata A. Walicka, Ph.D.

Patent Examiner

Art Unit 1652

REBECCA E. PROUTY
PRIMARY EXAMINER
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